Rapidly Evolving Extensive Fluorodeoxyglucose-Positive Soft-Tissue Activity During Nivolumab Therapy

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DOI: https://doi.org/10.1001/jamaoncol.2018.6431

JAMA Oncology Clinical Challenge

Rapidly Evolving Extensive Fluorodeoxyglucose-Positive Soft-Tissue Activity During Nivolumab Therapy

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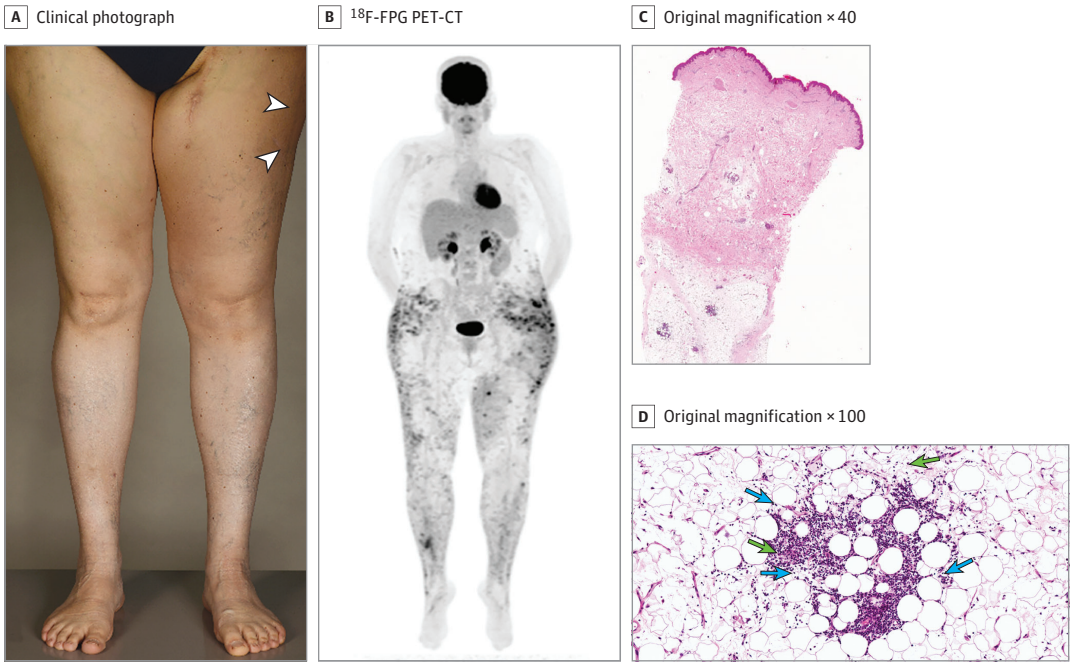

Figure. A, Localized erythematous brownish induration seen on the upper thigh. Arrowheads correlate with the most prominent clinical findings. B, Radioactive fluorine 18 (^{18}F) fluorodeoxyglucose (FDG) positron emission tomography–computed tomography (PET-CT) reveals multiple subcutaneous lesions in both lower extremities, the lumbar region, and on the ipsilateral lower leg with high FDG uptake highly suggestive of (in transit) metastasis. C and D, Lesional skin biopsy samples obtained from the proximal left thigh show normal epidermis and dermis with patchy infiltrate of the deep subcutaneous fat (hematoxylin-eosin stain). Green arrows indicate the plasma cells, and blue arrows indicate the lymphocytes.

A 41-year-old woman with a history of Hodgkin disease in her adolescence was diagnosed with melanoma of the left upper thigh that was classified as American Joint Committee on Cancer (AJCC) stage IIA with (pT3aN0 [sn0/1] M0) *BRAF* mutation. One year later she underwent inguinal lymphadenectomy for macrometastasis followed by adjuvant immunotherapy with ipilimumab, a monoclonal antibody that targets cytotoxic T-lymphocyte antigen 4. Owing to local disease progression, treatment escalation with combined immunotherapy (ipilimumab and nivolumab, an anti–PD-1 [programmed cell death 1]) antibody was initiated. Apart from immunotherapy-induced thyroiditis, the treatment was well tolerated. However, after 11 cycles of nivolumab, the patient presented with progressive painful reddening and swelling of the left thigh. There was no deterioration of the general condition, no fever, no change in current medication, and no recent cold exposure. Clinical examination revealed diffuse erythematous induration of the upper thigh expanding to the lower left abdominal area, as well as multiple small palpable subcutaneous nonindurated nodules on the ipsilateral gluteal region and leg (**Figure**, A). Fluorine 18 (^{18}F) fluorodeoxyglucose (FDG) positron emission tomography–computed tomography (PET-CT) detected multiple FDG-active lesions in both lower extremities and the lumbar region; a previously described left iliac lymphadenopathy was partially regressed (Figure, B). A diagnostic biopsy specimen of the left thigh revealed a lobular lymphocytic panniculitis with dense infiltrate of mainly lymphocytes and plasma cells with no signs of vasculitis (Figure, C and D). Direct immunofluorescence and blood analysis showed an absence of specific autoimmune antigens (test results for α-1 antitrypsin, antinuclear antibody, anti-Sjögren syndrome–related antigen, and anti-Sjögren syndrome–related antigen B were all unremarkable).

WHAT IS YOUR DIAGNOSIS?

A. Disease progression

B. Nivolumab-induced extensive panniculitis

C. Cold panniculitis

D. Erythema nodosum under nivolumab

Diagnosis

C. Nivolumab-induced extensive panniculitis

Discussion

Immunologic checkpoint blockade has changed the treatment landscape for advanced melanoma with impressive response and survival rates,[1] but it is associated with a large spectrum of immune-related toxic effects owing to an increase of the baseline T-cell–specific immune response.[2,3] Skin toxic effects represent the most common adverse effects associated with immune checkpoint inhibitors, including pruritus, rash, vitiligolike depigmentation, and lichenoid, cytotoxic, and autoimmune bullous reactions.[4] Interestingly, appearance of these adverse effects, especially vitiligo, is associated with a superior outcome and treatment response.[5]

Panniculitis is a group of inflammatory disorders of the subcutaneous fat tissue. Diagnosis can be challenging because different forms of panniculitis may present with overlapping clinical findings. Panniculitis can either be classified clinically based on the cause (eg, infection, inflammation, trauma, enzymatic destruction, deposition, or cancer) or histologically as lobular or septal panniculitis with or without concomitant vasculitis. As for drug-induced panniculitis, clinical and histopathological features of drug-induced panniculitis are indistinguishable from those associated with other agents, and only the history of previous drug intake or clinical improvement after drug treatment interruption may prove a causative relationship.[6]

Erythema nodosum (EN) is the most common type of panniculitis located on the anterior surface of the lower extremities. Mostly idiopathic in origin, EN may indicate an underlying systematic disease such as tuberculosis, deep bacterial and/or fungal infection, inflammatory bowel disease, or cancer. Erythema nodosum represents the cutaneous manifestation of sarcoidosis. Histologically, septal panniculitis can present without vasculitis and with radial granulomas. Erythema nodosum is also reported to be the most common drug-induced panniculitis.[7]

In the setting of immune checkpoint inhibitors used for cell-mediated immunity, few reports in the literature have described a sarcoidlike granulomatous panniculitis.[7-9] The typical histological pattern includes partly granulomatous reactions with mixed septal and lobular inflammatory infiltrate with lymphocytes and epithelioid histiocytes.

Herein, we report a case of lobular panniculitis without vasculitis. Lobular panniculitis is usually considered in connective tissue diseases, such as systemic lupus erythematosus, pancreatic diseases or α-1 antitrypsin deficiency. Other histopathologic differential diagnoses include infection, trauma, or subcutaneous T-cell lymphoma.[10] All of these differential diagnoses were ruled out through diagnostic workup in the present case. The absence of tumor cells in the biopsy specimen ruled out disease progression.

The treatment with nivolumab was continued unchanged, and the patient achieved a complete metabolic response seen in the routine follow-up ^{18}F-FDG PET-CTs. As for the panniculitis, the lesion regressed slowly without the need for systemic steroid or treatment cessation.

With regard to the treatment approach for immunotherapy-induced panniculitis, the lesions usually regress spontaneously or after treatment with nonsteroidal anti-inflammatory drugs or oral or topical steroids. Cessation of immunotherapy is not generally necessary.

To our knowledge, this is the first case of an extensive lobular panniculitis in a patient treated with an anti–PD-1 antibody. Until recently, panniculitides associated with immunotherapeutic agents have not been extensively described. Because inconclusive FDG-avid lesions may simulate disease progression, recognition of these adverse effects is important, and histopathological workup is mandatory to ensure adequate treatment and prevent unnecessary treatment discontinuation.

ARTICLE INFORMATION

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Published Online: January 24, 2019. doi:10.1001/jamaoncol.2018.6431

Conflict of Interest Disclosures: Dr Mangana reports a temporary advisory relationship and receives travel support from Merck Sharp & Dohme, Merck, and Pfizer. Dr Dummer reports research funding to the University of Zürich from Novartis, Merck Sharp & Dohme, Bristol-Myers Squibb, Roche, and GlaxoSmithKline and serves as a consultant or advisory board member for Novartis, Merck Sharp & Dohme, Bristol-Myers Squibb, Roche, GlaxoSmithKline, Amgen, and Takeda. No other disclosures were reported.

Additional Information: Drs Mangana and Buset contributed equally as co-first authors.

Additional Contributions: We thank the patient for granting permission to publish this information.

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